

**PRODUCT MONOGRAPH**

**CLORAZEPATE**

**(Clorazepate dipotassium Capsules)**

**Anxiolytic-Sedative**

**AA PHARMA INC.**

**1165 Creditstone Road, Unit #1  
Vaughan, Ontario  
L4K 4N7**

**Control Number: 156856**

**DATE OF PREPARATION:**

**September 16, 2020**

## **PRODUCT MONOGRAPH**

CLORAZEPATE

Clorazepate dipotassium capsules

## **THERAPEUTIC CLASSIFICATION**

Anxiolytic-Sedative

## **ACTIONS AND CLINICAL PHARMACOLOGY**

CLORAZEPATE (clorazepate dipotassium) possesses anxiolytic and sedative properties that have been found to be of value for the symptomatic relief of pathological anxiety and tension states in psychoneurotic patients.

Following ingestion, the drug is rapidly decarboxylated to form nordiazepam (N-desmethyldiazepam) which is absorbed rapidly and is the primary active metabolite. Peak serum levels of nordiazepam appear in from 1 to 2 hours following a single dose and the serum half-life is about 48 hours. During multiple dosage with clorazepate steady-state plasma concentrations of nordiazepam are usually attained in 5 days to 2 weeks. The concurrent use of antacids with clorazepate may decrease the rate and extent of conversion of the drug to desmethyldiazepam resulting in a small reduction (12%) in drug bioavailability. Subsequent hydroxylation of nordiazepam in the liver leads to the formation of oxazepam and p-OH-nordiazepam, which are excreted in the urine in conjugated and unconjugated forms. In man, approximately 52% of the urine drug level is found to be conjugated oxazepam. In 2 volunteers given 15 mg of <sup>14</sup>C-clorazepate, about 80% was recovered in the urine and faeces within 10 days. Excretion was primarily in the urine with about 1% excreted per day on day 10.

Clorazepate produces electroencephalographic changes similar to those of some of the other benzodiazepines, with an increased average frequency, frequency deviation and fast beta activity, while alpha activity and amplitudes decrease. In electroencephalographic studies of sleep, clorazepate produced decreased deep sleep stages with REM activity attenuated, although not significantly.

### **INDICATIONS**

CLORAZEPATE (clorazepate dipotassium) is indicated for the short-term symptomatic relief of excessive anxiety and tension in psychoneurotic patients including those with functional somatic complaints.

Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

It is also useful in the adjunctive management of acute alcohol withdrawal.

### **CONTRAINDICATIONS**

CLORAZEPATE is contraindicated in patients with myasthenia gravis and with known hypersensitivity to clorazepate dipotassium.

### **WARNINGS**

CLORAZEPATE (clorazepate dipotassium) is not recommended for use in depressive neuroses or in psychotic reactions.

Because of the lack of sufficient clinical experience, clorazepate dipotassium is not recommended for use in patients less than 18 years of age.

Since clorazepate dipotassium has a central nervous system depressant effect, patients should be advised against the simultaneous use of other CNS depressant drugs and cautioned that the effects of alcohol may be increased.

Patients on clorazepate dipotassium should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating dangerous machinery, including motor vehicles.

#### Use in Pregnancy

The safety of use of clorazepate dipotassium in pregnancy has not been established. Therefore, CLORAZEPATE is not recommended for use during pregnancy or lactation. Nordiazepam, the active metabolite of clorazepate, crosses the human placenta and is excreted in human breast milk. Several studies have suggested an increased risk of congenital malformations associated with the use of the benzodiazepines, chlordiazepoxide and diazepam, and meprobamate, during the first trimester of pregnancy. Malformations in the infant of a mother who had taken clorazepate during the first trimester of pregnancy has been reported. Since clorazepate dipotassium is also a benzodiazepine derivative, its administration is rarely justified in women of child-bearing potential. If the drug is prescribed to a woman of child-bearing potential, she should be warned to consult her physician regarding the discontinuation of the drug if she intends to become or suspects that she is pregnant.

## **PRECAUTIONS**

### **Use in Mental and Emotional Disorders**

Benzodiazepines, such as CLORAZEPATE, are not recommended in the treatment of psychotic or severely depressed patients. It should be recognized that suicidal tendencies may be present and that protective measures may be necessary. Since excitement and other paradoxical reactions may result from the use of the drug in psychotic patients, it should not be used in ambulatory patients suspected of having psychotic tendencies. Patients on CLORAZEPATE for prolonged periods should have blood counts and liver function tests periodically. The usual precautions in treating patients with impaired renal or hepatic function should also be observed.

### **Potential of Drug Effects**

If CLORAZEPATE is to be combined with other drugs acting on the central nervous system, careful consideration should be given to the pharmacology of the agents to be employed. Animal experience indicates that clorazepate prolongs the sleeping time after hexobarbital or after ethyl alcohol, increases the inhibitory effects of chlorpromazine, but does not exhibit monoamine oxidase inhibition. Clinical studies have shown increased sedation with concurrent hypnotic medications. The action of the benzodiazepines may be potentiated by barbiturates, narcotics, phenothiazines, monoamine oxidase inhibitors, or other antidepressants.

### **Dependence Liability**

CLORAZEPATE (clorazepate dipotassium) should not be administered to individuals prone to drug abuse. Caution should be observed in patients who are considered to have potential for psychological dependence. Withdrawal symptoms similar to those occurring with this category of

drugs have been observed after abrupt discontinuation of clorazepate. Symptoms of insomnia, nervousness, irritability, muscle aches, diarrhea, tremor, and memory impairment were reported after abrupt withdrawal of large doses of clorazepate taken for prolonged periods.

### Use in the Elderly

Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to CNS depression after even low doses of benzodiazepines. Therefore, medication should be initiated in these patients with very low initial doses, and increments should be made gradually, depending on the response of the patient, in order to avoid oversedation or neurological impairment.

### Narrow-angle Glaucoma

CLORAZEPATE should be given with caution, if at all, to patients with acute narrow-angle glaucoma.

## **ADVERSE REACTIONS**

The side effect most frequently reported is drowsiness. Less commonly reported (in descending order of occurrence) are: dizziness, various gastrointestinal complaints, nervousness, blurred vision, dry mouth, headache and mental confusion. Other side effects include insomnia, transient skin rashes, fatigue, ataxia, genito-urinary complaints, irritability, diplopia, depression, slurred speech and hypotension.

There have been reports of abnormal liver and kidney function tests and of a decrease in hematocrit. Decrease in systolic blood pressure has been observed with clorazepate.

## **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

### Symptoms

Clorazepate dipotassium overdose may be manifested by varying degrees of CNS depression ranging from drowsiness, confusion, ataxia to coma. Hyporeflexia may occur. Unless the overdose is extreme, effects on pulse, blood pressure and respiration are minimal.

### Treatment

There are no specific antidotes for clorazepate. The treatment of overdose should consist of the general measures employed in the management of overdose of any CNS depressant.

If vomiting has not occurred spontaneously and the patient is fully awake, it may be induced with syrup of ipecac 20 to 30 mL. Gastric lavage should be considered as soon as possible and 50 to 100 g of activated charcoal should be introduced and left in the stomach.

Hypovolemia, indicated by reduced central venous pressure, should be treated, if present, with a balanced salt solution.

Although hypotension is rarely reported, it may occur with large overdoses and in this situation the use of pressor agents, such as levarterenol or metaraminol, should be considered.

## **DOSAGE AND ADMINISTRATION DOSAGE**

### DOSAGE

The dosage of CLORAZEPATE (clorazepate dipotassium) must be individualized and carefully titrated in order to avoid excessive sedation or mental and motor impairment.

As with other anxiolytic sedatives, short courses of treatment should usually be the rule for the symptomatic relief of disabling anxiety in psychoneurotic patients and the initial course of treatment should not last longer than 1 week without reassessment of the need for a limited extension. Initially, not more than 1 week's supply of the drug should be provided and automatic prescription renewals should not be allowed. Subsequent prescriptions, when required, should be limited to short courses of therapy.

CLORAZEPATE (clorazepate dipotassium) is administered orally in divided doses. The usual adult daily dose is 30 mg. The dose should be adjusted gradually within the range of 15 to 60 mg in accordance with the response of the patient. After the patient has been stabilized on a suitable dosage, the frequency of dosing may be decreased in some patients to twice daily or once daily with the major portion of the dosage given at night, provided that the physician can ascertain that such a schedule will produce the desired anxiolytic effect without a period of drowsiness or impairment of mental functions.

#### Elderly or Debilitated Patients

In these patients, treatment should be initiated with 3.75 mg once a day, preferably at night. The dosage should be very carefully and gradually adjusted, depending on tolerance and response.

For the management of acute alcoholic withdrawal, the following dosages may be used: 30-90 mg in divided doses in the first 24 hours, depending on individual tolerance and response. In the second 24 hours, the dosage should be reduced to not more than 60 mg in divided doses. Subsequently, the daily dosage should be reduced gradually, usually to not more than 15-30 mg on the 4th day, and should then be tapered off more rapidly and discontinued as soon as possible.



Since anxiolytic sedatives are indicated for the treatment of current or state anxiety, administration of CLORAZEPATE should generally be limited to the duration of the episode requiring symptomatic relief.

## **AVAILABILITY**

### **Storage and Stability**

Store at room temperature (15-25°C) in a tightly closed container.

Keep out of reach and sight of children.

### **Dosage forms, composition and packaging**

Each CLORAZEPATE 3.75 mg capsule contains 3.75 mg of clorazepate dipotassium. Each 3.75 mg hard gelatin capsule consists of an iron gray opaque body and a white opaque cap, imprinted 3.75 in black pharmaceutical ink.

Each CLORAZEPATE 7.5 mg capsule contains 7.5 mg of clorazepate dipotassium. Each 7.5 mg hard gelatin capsule consists of an iron gray body and maroon opaque cap, imprinted 7.5 in black pharmaceutical ink.

Each CLORAZEPATE 15 mg capsule contains 15 mg of clorazepate dipotassium. Each 15 mg hard gelatin capsule consists of an iron gray opaque body and cap, imprinted 15 in black pharmaceutical ink.

### **Non-Medicinal Ingredients**

CLORAZEPATE, 3.75 mg capsule fill contains lactose monohydrate, cornstarch and stearic acid.

The following are the capsule shell ingredients: black iron oxide, titanium dioxide, gelatin and pharmaceutical ink.

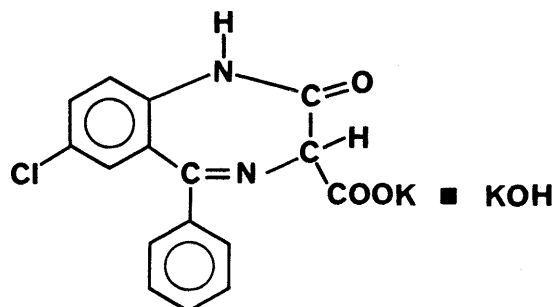
CLORAZEPATE, 7.5 mg capsule fill contains lactose monohydrate, cornstarch and stearic acid. The following are the capsule shell ingredients: black iron oxide, titanium dioxide, gelatin, D&C red #33, D&C yellow #10 and pharmaceutical ink.

CLORAZEPATE, 15 mg capsule fill contains lactose monohydrate, cornstarch, stearic acid. The following are the capsule shell ingredients: black iron oxide, titanium dioxide, gelatin and pharmaceutical ink.

CLORAZEPATE is supplied as capsules, in bottles of 100, 500 and 1000.

## CHEMISTRY AND PHARMACOLOGY

Clorazepate dipotassium is a benzodiazepine and has the following structural formula:



Molecular Formula:  $C_{16}H_{11}Cl K_2N_2O_4$

Molecular Weight: 408.9

Clorazepate dipotassium has central nervous system depressant properties with a somewhat flatter dose-response curve than the sedative-hypnotic drugs.

Studies in laboratory animals showed that clorazepate dipotassium produced, in varying doses, taming, disinhibitory, sedative, anti-convulsant, muscle-relaxant, ataxic and hypnotic effects.

As with the sedative hypnotic drugs, benzodiazepines at sedative doses reduce slightly behavioural arousal, increase responsiveness to environmental stimuli, suppress passive avoidance behaviour, and increase approach behaviour. At slightly higher doses, they appear to increase errors of commission in performing tasks, produce drowsiness and ataxia, and decrease muscle tone. At low doses, clorazepate dipotassium does not reduce significantly locomotor activity.

Clorazepate dipotassium suppresses pentylenetetrazol-induced convulsions, but is relatively ineffective against maximal electroshock convulsions.

Clorazepate dipotassium has shown little or no effect on the autonomic nervous system.

After treatment of rats for one week, there was no indication that clorazepate dipotassium enhanced the activity of liver microsomal enzymes. It, however, possesses dependence liability and may produce withdrawal symptoms, but has a wide margin of safety against poisoning.

In rats, conditioned avoidance response was inhibited at an oral dose of 10 mg/kg and sedation was induced at 32 mg/kg. In monkeys, aggressive behaviour was reduced at an oral dose of 0.25 mg/kg and sedation (ataxia) was induced at 7.5 mg/kg.

## **TOXICOLOGY**

### Acute Toxicity:

Animal Species	Sex	Oral LD <sub>50</sub> (and 95% probability level inclusive of the 20% confidence limits) mg/kg
Mice*	F	2025 (1633-2511)
	M	1850 (1394-2456)
	Combined	1915 (1655-2216)
Rats*	F	1360 (1048.9-1763.3)
	M	1650 (1427.7-1907.0)
	Combined	1440 (1299.7-1595.5)

\* 9 groups, each with 5 animals/sex were treated with the test article (clorazepate dipotassium) at logarithmically spaced doses.

Mortality generally occurred over a 48 hour period post-dosing.

Signs of systemic toxicity were ptosis, reduced activity and ataxia, piloerection, dyspnea or bradypnea, epistaxis, lacrimation, perineal staining, hunchback and coma.

Necropsy of these animals generally revealed darkening of the liver, paleness of the kidney

and/or spleen, distension and/or irritation/hemorrhage of the stomach and or small intestine, distention of the urinary bladder and pulmonary congestion. Animals killed routinely at the conclusion of the study generally revealed no abnormality.

### Subacute Toxicity Studies

#### Rats

It has been reported that rats could tolerate 50 times the human dose of clorazepate dipotassium administered daily by intubation for 78 weeks except for sedation, muscle relaxation and drowsiness. At higher doses (100 to 150 times the human dose) these effects were more marked. Pituitary chromophobe adenomatous hyperplasia in 4 of 10 females was also observed at higher doses.

#### Dogs

A 22 month oral chronic toxicity study in 24 dogs involving doses up to 75 mg/kg/day indicated that dogs could tolerate about 20 times the human dose of clorazepate dipotassium except for sedation, weight gain and reversible liver function disturbance. Higher doses produced more severe sedation and liver function disturbance. Liver mass increase and hepatic canalicular bile stasis without evidence of obstruction were observed at necropsies.

#### Monkeys

Rhesus monkeys (18) given increasing oral doses (from 3 mg/kg to 36 mg/kg/day) of clorazepate dipotassium could tolerate 18 to 36 times the human dose daily for 52 weeks. No significant differences were found between treated and control groups. Although total leukocyte count remained within normal limits it tended to fall in female monkeys at the highest doses.

Examination of all organs revealed no alterations attributable to the drug. No alteration of liver function or structure was observed.

### Reproductive Studies

Fertility, reproduction and teratology studies in rats at doses up to 150 mg/kg/day and in rabbits at doses up to 15 mg/kg/day produced no abnormalities in the fetuses. An increased resorption was observed in the rabbits and retarded ossification in the fetuses of the treated higher dose dams. Clorazepate dipotassium did not alter the fertility indices or reproductive capacity of adult animals. The sedative effect of higher doses interfered with the care of the young by their mothers.

## **BIBLIOGRAPHY**

1. Burrows GD, Dumovic P, Smith JA, Norman T, Maguire K: A controlled comparative trial of clorazepate (Tranxene) and diazepam (Valium) for anxiety. *Med J Aust* 1977; 2: 525-528.
2. Charalampous KD, Tooley W, Yates C: Clorazepate dipotassium: a new benzodiazepine anti-anxiety agent. *J Clin Pharmacol* 1973; 13: 114-118.
3. Chun AHC, Carrigan PJ, Hoffman DJ, Kershner RP, Stuart JD: Effect of antacids on absorption of clorazepate. *Clin Pharmacol Ther* 1977; 22: 329-335.
4. Cohen AR, Levin A, Houlton PJC, Wolhuter A: The use of clorazepate for premedication on the night before surgery. *Br. J Anaesth* 1978; 50: 821-823.
5. Cooper AJ, Magnus RV, Rose M, Phanjoo A, Lancaster NP, Pollard P, Knowlson P: Controlled trial of dipotassium clorazepate in anxiety. *Br J Psychiat* 1973; 123: 475-476.
6. Fabre LF, McLendon DM, Mallette A: A double blind comparison of prazepam with diazepam, clorazepate dipotassium and placebo in anxious out-patients. *J Int Med Res* 1979; 7: 147-151.
7. Feurst SI: Clorazepate dipotassium, diazepam, and placebo in chronic anxiety. *Curr Ther Res* 1973; 15: 449-459.
8. Greenblatt DJ, Shader RI: Pharmacokinetic aspects of anxiolytic drug therapy. *Can J Neurol Sci* 1980; 7: 269-270.
9. Guerre-Millo M, Rey E, Challier JC, Turquais JM, d'Athis P, Olive G: Transfer in vitro of three benzodiazepines across the human placenta. *Eur J Clin Pharmacol* 1979; 15: 171-173.
10. Harris PG: Patient acceptance as a factor in the effectiveness of treatment: an assessment of potassium clorazepate (Tranxene) and lorazepam in anxiety. *Curr Med Res Opin* 1975; 2: 664-668.
11. Holmberg G, Livstedt B: Clinical evaluation of a new benzodiazepine derivative, chlorazepate. *Arzneim-Forsch* 1972; 22: 916-919.
12. Itil TM, Saletu B, Marasa J: Digital computer analyzed sleep electroencephalogram (sleep prints) in predicting anxiolytic properties of clorazepate dipotassium (Tranxene). *Curr Ther Res* 1972; 14: 415-427.
13. Lossius R, Dietrichson P, Lunde PKM: Effect of clorazepate in spasticity and rigidity: a quantitative study of reflexes and plasma concentrations. *Acta Neurol Scand* 1985; 71: 190-194.
14. Magnus RV: Once-a-day potassium clorazepate in anxiety. *Br J Clin Pract* 1973; 27: 449-452.

15. Ochs HR, Greenblatt DJ, Allen MD, Harmatz JS, Shader RI, Bodem G: Effect of age and Billroth gastrectomy on absorption of desmethyldiazepam from clorazepate. *Clin Pharmacol Ther* 1979; 26: 449-456.
16. Patel DA, Patel AR: Clorazepate and congenital malformations. *JAMA* 1980; 244: 135-136.
17. Rey E, Giraux P, d'Athis P, Turquais JM, Chavinie J, Olive G: Pharmacokinetics of the placental transfer and distribution of clorazepate and its metabolite nordiazepam in the fetoplacental unit and in the neonate. *Eur J Clin Pharmacol* 1979; 15: 181-185.
18. Ricca JJ: Clorazepate dipotassium in anxiety: a clinical trial with diazepam and placebo controls. *J Clin Pharmacol* 1972; 12: 286-290.
19. Saletu B, Saletu M, Itil TM: Somatosensory evoked potential: an objective indicator of the therapy efficacy of a new psychotropic drug, clorazepate dipotassium (Tranxene). *Curr Ther Res* 1972; 14: 428-441.
20. Shader RI, Georgotas A, Greenblatt DJ, Harmatz JS, Allen MD: Impaired absorption of desmethyldiazepam from clorazepate by magnesium aluminum hydroxide. *Clin Pharmacol Ther* 1978; 24: 308-315.
21. Shader RI, Greenblatt DJ, Ciraulo DA, Divoll M, Harmatz JS, Georgotas A: Effect of age and sex on disposition of desmethyldiazepam formed from its precursor clorazepate. *Psychopharmacol* 1981; 75: 193-197.
22. Wilensky AJ, Levy RH, Troupin AS, Moretti-Ojemann L, Friel P: Clorazepate kinetics in treated epileptics. *Clin Pharmacol Ther* 1978; 24: 22-30.